PATENT COOPERATION TREATY

09998013

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 January 2001 (12.01.01)	
International application No. PCT/EP00/03842	**Applicant's or agent's file reference** JEC/FP5847868
International filing date (day/month/year) 27 April 2000 (27.04.00)	**Priority date** (day/month/year) 03 May 1999 (03.05.99)
Applicant ARENAS, Ernest et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   24 November 2000 (24.11.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
JEC/FP5847868		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/03842	27/04/2000	03/05/1999
Applicant		
KAROLINSKA INNOVATIONS AB et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/03842

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 28-31, 40-49, 52-59
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 28-31, 40-49, 52-59

Since the claims are not part of a method of screening, but in fact cover the pharmaceutical formulation and therapeutic use of the agents/factors/substances resulting from the respective methods of screening, they have been interpreted as pharmaceutical formulation and therapeutic use claims, independent from the method of screening.

Present claims 28-31, 40-49 and 52-59 respectively relate to agents/factors/substances defined by reference to a desirable characteristic or property, namely respectively: improvement of neuron recovery, induction of dopaminergic fate in Nurr++ stem cells and modulation of the ability of type-1 astrocytes to induce dopaminergic fate in Nurr1++ stem cells.

The claims cover all agents/factors/substances having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such agents/factors/substances. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agents/factors/substances by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03842

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/06 C12N5/08 C12N5/10 A61K35/30 G01N33/50
C12Q1/68 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E. ARENAS ET AL.: "Nurr1 overexpression enriches for neuronal phenotype in multipotent, neural stem-like cells." SOCIETY FOR NEUROSCIENCE ABSTRACTS, 28TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 2, LOS ANGELES, US, NOVEMBER 7-12, 1998, vol. 24, 1998, page 1531 XP000961113 abstract nr. 606.10 ---	1,3,22
X	WO 96 15224 A (NEUROSPHERES HOLDINGS, LTD) 23 May 1996 (1996-05-23) page 6, line 18 -page 7, line 11; claims; examples 9,10,12,13 page 13, line 1 -page 17, line 23 --- -/--	14-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2000	09. 01. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 09543 A (NEUROSPHERES LTD.) 28 March 1996 (1996-03-28) page 13, line 25 -page 16, line 5; claims; examples 3,4 ---	25-59
A	D.M. PANCHISION ET AL.: "An immortalized, type-1 astrocyte of mesencephalic origin source of a dopaminergic neurotrophic factor." JOURNAL OF MOLECULAR NEUROSCIENCE, vol. 11, no. 3, 1998, pages 209-221, XP000971060 page 210, right-hand column, paragraph 2 ---	1-59
A	T. TAKESHIMA ET AL.: "Astrocyte-dependent and -independent phases of the development and survival of rat embryonic day 14 mesencephalic, dopaminergic neurons in culture." NEUROSCIENCE, vol. 60, no. 3, 1994, pages 809-823, XP000971036 oxford, gb page 821, right-hand column, paragraph 2 ---	1-59
A	A. GRITTI ET AL.: "Basic fibroblast growth factor supports the proliferation of epidermal growth factor-generated neuronal precursors cells of the adult mouse CNS." NEUROSCIENCE LETTERS, vol. 185, no. 3, 1995, pages 151-154, XP000961084 amsterdam, nl page 153, right-hand column, paragraph 2 -page 154, left-hand column, paragraph 1 ---	1-59
A	O. SAUCEDO-CARDENAS ET AL.: "Nurr1 is essential for the induction of the dopaminergic phenotype and the survival of ventral mesencephalic late dopaminergic precursor neurons." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, March 1998 (1998-03), pages 4013-4018, XP002154886 WASHINGTON US page 4017, left-hand column, line 3 -right-hand column, paragraph 1 --- -/--	1-59

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J. WAGNER ET AL.: "Induction of a midbrain dopaminergic phenotype in Nurr1-overexpressing neural stem cells by type 1 astrocytes." NATURE BIOTECHNOLOGY, vol. 17, July 1999 (1999-07), pages 653-659, XP002154887 london, gb the whole document ---	1-24
P,A	K. SAKURADA ET AL.: "Nurr1, an orphan nuclear receptor, is a transcriptional activator of endogenous tyrosine hydroxylase in neural progenitor cells derived from the adult brain." DEVELOPMENT, vol. 126, September 1999 (1999-09), pages 4017-4026, XP002929722 page 4018, left-hand column, paragraph 2 page 4022, left-hand column, line 11 - line 60 -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/03842

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9615224 A	23-05-1996	US 5981165 A	09-11-1999
		AU 715246 B	20-01-2000
		AU 3836695 A	06-06-1996
		CN 1170434 A	14-01-1998
		EP 0792349 A	03-09-1997
		FI 971955 A	03-07-1997
		JP 10509319 T	14-09-1998
		NO 972170 A	30-06-1997
WO 9609543 A	28-03-1996	AU 714837 B	13-01-2000
		AU 3515295 A	09-04-1996
		CA 2200709 A	28-03-1996
		EP 0783693 A	16-07-1997
		FI 971168 A	20-03-1997
		JP 10505754 T	09-06-1998
		NO 971245 A	18-03-1997
		US 6071889 A	06-06-2000
		US 5750376 A	12-05-1998
		US 5980885 A	09-11-1999
		US 5851832 A	22-12-1998

WO 00/66713
PCT/EP00/03842

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
WALTON, Seán, M.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

20 NOV 2000

Date of mailing (day/month/year) 09 November 2000 (09.11.00)	
Applicant's or agent's file reference JEC/FP5847868	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/03842	27 April 2000 (27.04.00)	03 May 1999 (03.05.99)

Applicant
KAROLINSKA INNOVATIONS AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   09 November 2000 (09.11.00) under No. WO 00/66713

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II h... right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 ... or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected ...

For further important information on the time limits and acts to be performed for entering the national phase, ... Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMW/FP5847868		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03842	27/04/2000	03/05/1999
International Patent Classification (IPC) or national classification and IPC C12N5/00		
Applicant KAROLINSKA INNOVATIONS AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/11/2000	28.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wimmer, G Telephone No. +49 89 2399 7347

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03842

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-44	as originally filed	

Claims, No.:

58,59	as originally filed	
1-57	with telefax of	15/06/2001

Drawings, sheets:

1/3-3/3	as originally filed	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 25-28, 31, 38-47, 50-57 (entirely), 13-15 with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 13-15 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28-31, 40-49, 52-59.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24, 29, 30, 32-37, 48, 49
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-24, 29, 30, 32-37, 48, 49
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12, 16-24, 29, 30, 32-37, 48, 49
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion.

1) Amended claims 25-28, 31, 38-47, and 50-57 are directed to pharmaceutical formulations and therapeutic uses of agents which are only defined through resulting from screening processes (see also the International Search Report for corresponding original claims). Since it is well possible that factors, which could result from such screening methods, are already known and used for such purposes, no meaningful examination can be performed for these claims. Therefore, no opinion on novelty, inventive step, and industrial applicability of present claims 25-28, 31, 38-47, and 50-57 is given herein.

2) Claims 13-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability.

1) Reference is made to the following documents (the document numbering corresponds to their order of citation in the international search report):

D1: E. ARENAS ET AL.: 'Nurr1 overexpression enriches for neuronal phenotype in multipotent, neural stem-like cells.' SOCIETY FOR NEUROSCIENCE ABSTRACTS, 28TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 2, LOS ANGELES, US, NOVEMBER 7-12, 1998, vol. 24, 1998, page 1531 XP000961113

D2: WO 96 15224 A (NEUROSPHERES HOLDINGS, LTD) 23 May 1996 (1996-05-23)

Novelty under Art. 33(2) PCT.

2) Although methods of the prior which aim to induce a dopaminergic phenotype from non-dopaminergic neural tissue include the overexpression of *Nurr1* (D1) and the use of astrocytes as feeder cells (D2), no method was disclosed combining *Nurr1* overexpression, and the use of factors derived from Type 1 astrocytes of the ventral mesencephalon.

Methods and entities which include, or result from, such a combination of methods, are therefore novel.

Claims 1-24, 29, 30, 32-37, 48, and 49 therefore comply with art. 33(2) PCT.

Inventive Step under Art. 33(3) PCT.

7) Concerning claim 1, Document D1 can be viewed to be the prior art. D1 describes the attempt to induce the differentiation of neural progenitor cells to dopaminergic neurons through overexpression of Nurr1. D1 states that this has been only partly successful, since Nurr1 expressing cells developed a neuronal phenotype, but no tyrosine hydroxylase expression. D1 states that additional factors may be necessary to further restrict these cells to dopaminergic cell fates.

D2 describes experiments to induce dopaminergic cells from non-dopaminergic neural tissue. In this, the authors find that contacting the cells with Fibroblast Growth Factor leads to the efficient induction of dopaminergic cells. Furthermore, the authors also used astrocytes as feeder cells for the neural cells, and found that a combination of FGF and factors from astrocytes leads to highest induction of the desired phenotype.

It would therefore be possible to combine the methods of D1 and D2, to arrive at the methods and entities of the current application.

However, the IPEA concurs with the applicants' arguments, that D2 does not identify factors which are capable of restricting neuronal cells to a dopaminergic fate. Rather, stem cells used as starting material in the experiments of D2 were taken from tissue which can be expected to at least partially contain cells already committed to a dopaminergic fate, and therefore the method of D2 can be viewed as one to enhance the survival and differentiation of such cells.

In the opinion of the IPEA, it is not evident if the method of D1 (*Nurr1* overexpression) allows for the differentiation of the C17.2 cells used therein, to neural cells comparable to the starting material in the methods of D2. The use of *Nurr1* overexpression and of factors from type-1 astrocytes of the ventral mesencephalon, to induce a dopaminergic phenotype in a cell not committed to a dopaminergic cell fate, can therefore be viewed to involve an inventive step.

Claims 1-24, 29, 30, 32-37, 48, and 49 therefore comply with art. 33(3) PCT.

Industrial Applicability under Art. 33(4) PCT.

12) For the assessment of the present claims 13-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12N 5/00 | A2

(11) International Publication Number: WO 00/66713

(43) International Publication Date: 9 November 2000 (09.11.00)

(21) International Application Number: PCT/EP00/03842

(22) International Filing Date: 27 April 2000 (27.04.00)

(30) Priority Data:
60/132,317 3 May 1999 (03.05.99) US

(71) Applicant *(for all designated States except US)*: KAROLINSKA INNOVATIONS AB [SE/SE]; Tomtebodavägen 11, F, Solna, S–171 77 Stockholm (SE).

(72) Inventors; and

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(54) Title: MATERIALS AND METHODS RELATING TO NEURONAL DEVELOPMENT

(57) Abstract

The invention relates to the induction of the neuronal fate in neural stem cells or neural progenitor cells. The inventors have found that a neuronal fate in a neural stem cell or neural progenitor cell can be induced by expressing Nurr1 above basal levels within the cell. *Nurr*1 is a transcription factor of the thyroid hormone/retinoic acid nuclear receptor superfamily. It is shown herein that the expression of *Nurr*1 above basal levels in neural stem cells or neural progenitor cells increases the proportion of the cells which differentiate toward a neural fate. It has been found that in particular, dopaminergic neural stem cells or progenitor cells by a process including expression of *Nurr*1 above basal levels in the cells and contact of the cells with one or more factors supplied by or derived from Type I astrocytes of the ventral mesencephalon.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/03842

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/06 C12N5/08 C12N5/10 A61K35/30 G01N33/50
C12Q1/68 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E. ARENAS ET AL.: "Nurr1 overexpression enriches for neuronal phenotype in multipotent, neural stem-like cells." SOCIETY FOR NEUROSCIENCE ABSTRACTS, 28TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 2, LOS ANGELES, US, NOVEMBER 7-12, 1998, vol. 24, 1998, page 1531 XP000961113 abstract nr. 606.10 ---	1,3,22
X	WO 96 15224 A (NEUROSPHERES HOLDINGS, LTD) 23 May 1996 (1996-05-23) page 6, line 18 -page 7, line 11; claims; examples 9,10,12,13 page 13, line 1 -page 17, line 23 --- -/--	14-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2000	09 01 2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Ryckebosch, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 09543 A (NEUROSPHERES LTD.) 28 March 1996 (1996-03-28) page 13, line 25 -page 16, line 5; claims; examples 3,4 ---	25-59
A	D.M. PANCHISION ET AL.: "An immortalized, type-1 astrocyte of mesencephalic origin source of a dopaminergic neurotrophic factor." JOURNAL OF MOLECULAR NEUROSCIENCE, vol. 11, no. 3, 1998, pages 209-221, XP000971060 page 210, right-hand column, paragraph 2 ---	1-59
A	T. TAKESHIMA ET AL.: "Astrocyte-dependent and -independent phases of the development and survival of rat embryonic day 14 mesencephalic, dopaminergic neurons in culture." NEUROSCIENCE, vol. 60, no. 3, 1994, pages 809-823, XP000971036 oxford, gb page 821, right-hand column, paragraph 2 ---	1-59
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A	O. SAUCEDO-CARDENAS ET AL.: "Nurr1 is essential for the induction of the dopaminergic phenotype and the survival of ventral mesencephalic late dopaminergic precursor neurons." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, March 1998 (1998-03), pages 4013-4018, XP002154886 WASHINGTON US page 4017, left-hand column, line 3 -right-hand column, paragraph 1 --- -/--	1-59

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J. WAGNER ET AL.: "Induction of a midbrain dopaminergic phenotype in Nurr1-overexpressing neural stem cells by type 1 astrocytes." NATURE BIOTECHNOLOGY, vol. 17, July 1999 (1999-07), pages 653-659, XP002154887 london, gb the whole document ---	1-24
P,A	K. SAKURADA ET AL.: "Nurr1, an orphan nuclear receptor, is a transcriptional activator of endogenous tyrosine hydroxylase in neural progenitor cells derived from the adult brain." DEVELOPMENT, vol. 126, September 1999 (1999-09), pages 4017-4026, XP002929722 page 4018, left-hand column, paragraph 2 page 4022, left-hand column, line 11 - line 60 -----	1-24

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 00/03842

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 28-31, 40-49, 52-59
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 28-31, 40-49, 52-59

Since the claims are not part of a method of screening, but in fact cover the pharmaceutical formulation and therapeutic use of the agents/factors/substances resulting from the respective methods of screening, they have been interpreted as pharmaceutical formulation and therapeutic use claims, independent from the method of screening.

Present claims 28-31, 40-49 and 52-59 respectively relate to agents/factors/substances defined by reference to a desirable characteristic or property, namely respectively: improvement of neuron recovery, induction of dopaminergic fate in Nurr++ stem cells and modulation of the ability of type-1 astrocytes to induce dopaminergic fate in Nurr1++ stem cells.

The claims cover all agents/factors/substances having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such agents/factors/substances. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agents/factors/substances by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

al Application No
PCT/EP 00/03842

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WO 9615224 A	23-05-1996	US 5981165 A	09-11-1999
		AU 715246 B	20-01-2000
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		CN 1170434 A	14-01-1998
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		US 5851832 A	22-12-1998

CLAIMS:

1. A method of inducing a neuronal fate in a neural stem cell or neural progenitor cell, the method including expressing *Nurr1* above basal levels within the cell.

2. A method according to claim 1 comprising contacting the cell with FGF8.

3. A method according to claim 1 comprising transforming a neural stem cell or neural progenitor cell with *Nurr1*.

4. A method according to any one of claims 1 to 3 further comprising contacting the cell with one or more factors supplied by or derived from a Type 1 astrocyte.

5. A method according to claim 4 which comprises co-culturing the neural stem cell or neural progenitor cell with a Type 1 astrocyte.

6. A method according to claim 5 wherein the Type 1 astrocyte is immortalized or is of an astrocyte cell line.

7. A method according to claim 5 or claim 6 wherein the Type 1 astrocyte is of the ventral mesencephalon.

8. A method according to claim 7 wherein a dopaminergic fate is induced in said cell.

9. A method according to any one of claims 4 to 8 wherein said cell is mitotic when it is contacted with said one or more factors.

10. A method according to any one of claims 4 to 9 wherein said cell is additionally contacted with one or more agents selected from the group consisting of: basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), an activator of the retinoid X receptor (RXR), and 9-cis retinol.

11. A method according to any one of claims 4 to 10 wherein said cell is additionally contacted with a member of the FGF family of growth factors.

12. A method according to claim 11 wherein said cell is contacted with bFGF or EGF, and SR11237.

13. A method according to any one of claims 4 to 10 wherein the neural stem cell or neural progenitor cell is pretreated with bFGF and/or EGF prior to contacting the cell with one or more factors supplied by or derived from a Type 1 astrocyte.

14. A method according to any one of the preceding claims further comprising formulating a neuron produced by the method into a composition comprising one or more additional components.

15. A method according to claim 14 wherein the composition comprises a pharmaceutically acceptable excipient.

16. A method according to claim 15 further comprising administering the composition to an individual.

17. A method according to claim 16 wherein the neuron is implanted into the brain of the individual.

18. A method according to claim 17 wherein the individual has Parkinson's disease.

19. A method according to any of claims 1 to 13 further comprising use of a neuron produced in accordance with the method in the manufacture of a medicament for treatment of an individual.

20. A method according to claim 19 wherein the medicament is for implantation into the brain of the individual.

21. A method according to claim 20 wherein the individual has Parkinson's disease.

22. A neuron produced in accordance with any one of claims 1 to 13.

23. A composition comprising a neuron according to claim 22.

24. A composition according to claim 23 comprising one or more additional components.

25. Use of a neuron according to claim 22 in a method of screening for an agent for use in treatment of a neurodegenerative disease.

26. Use according to claim 25 comprising, or a method according to any one of claims 1 to 13 further comprising:

(i) treating a neuron with a toxin for said neuron;

(ii) separating the neuron from the toxin;

(iii) bringing the treated neuron into contact with a test agent or test agents;

(iv) determining the ability of the neuron to recover from the toxin;

(v) comparing said ability of the neuron to recover from the toxin with the ability of a neuron to recover from the toxin in the absence of contact with the test agent(s).

27. Use according to claim 25 comprising, or a method according to any one of claims 1 to 13 further comprising:

(i) treating a neuron with a toxin for the neuron in the presence of a test agent or test agents;

(ii) determining the ability of the neuron to tolerate the toxin;

(iii) comparing said ability of the neuron to tolerate the toxin with the ability of a neuron to tolerate the toxin in the absence of contact with the test agent(s).

28. Use, or a method according to claim 26 or claim 27 further comprising formulating an agent which improves ability of a neuron to recover from or tolerate a said toxin into a composition comprising one or more additional components.

29. Use, or a method according to claim 28 wherein said composition comprises a pharmaceutically acceptable excipient.

30. Use, or a method according to claim 29 further comprising administering said composition to an individual.

31. Use, or a method according to claim 30 wherein the individual has Parkinson's disease.

32. A method of screening for a factor or factors which, either alone or in combination, induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr*1 above basal levels, the method comprising:

(a) bringing a test substance into contact with a neural stem cell or neural progenitor cell expressing *Nurr*1 above basal levels, which contact may result in interaction between the test substance and the neural stem or progenitor cell; and

(b) determining interaction between the test substance and the stem or progenitor cell.

33. A method according to claim 32 which comprises contacting said cell with Type 1 astrocyte molecules.

34. A method according to claim 33 which comprises comparing molecules of Type 1 astrocytes of the ventral mesencephalon with those of neural cells which are unable to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr*1 above basal levels.

35. A method of screening for a factor or factors which, either alone or in combination, induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr*1 above basal levels, the method comprising culturing a neural stem cell or neural progenitor cell expressing *Nurr*1 above basal levels in the presence of a test substance or test substances and analyzing said cell for differentiation to a dopaminergic phenotype.

36. A method according to claim 34 which comprises culturing said cell with Type 1 astrocyte.

37. A method according to claim 36 which comprises comparing Type 1 astrocytes of the ventral mesencephalon

with neural cells which are unable to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr*1 above basal levels.

38. A method according to claim 37 which comprises differential expression screening.

39. A method according to any one of claims 32 to 38 wherein a factor or factors able to induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr*1 above basal levels is or are provided in isolated and/or purified form.

40. A method according to any one of claims 32 to 39 wherein a factor or factors able to induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr*1 above basal levels is or are formulated into a composition comprising one or more additional components.

41. A method according to claim 40 wherein the composition comprises a neural stem or progenitor cell expressing *Nurr*1 above basal levels.

42. A method according to claim 40 or claim 41 wherein the composition comprises a pharmaceutically acceptable excipient.

43. A method according to claim 42 further comprising administering the composition to an individual.

44. A method according to claim 43 wherein the composition is implanted into the brain of the individual.

45. A method according to claim 44 wherein the

individual has Parkinson's disease.

46. A method according to any one of claims 32 to 39 further comprising use of a factor or factors able to induce a dopaminergic fate in a neural stem or progenitor cell expressing *Nurr*1 above basal levels in the manufacture of a medicament for treatment of an individual.

47. A method according to claim 46 wherein the medicament comprises a neural stem or progenitor cell expressing *Nurr*1 above basal levels.

48. A method according to claim 46 or claim 47 wherein the medicament is for implantation into the brain of the individual.

49. A method according to claim 48 wherein the individual has Parkinson's disease.

50. A method of screening for a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules of such astrocytes, to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr*1 above basal levels, the method comprising:

(i) co-culturing Type 1 astrocytes with neural stem or progenitor cells which express *Nurr*1 above basal levels in the presence of one or more test substances; or

(ii) bringing neural stem or progenitor cells which express *Nurr*1 above basal levels into contact with one or more molecules of Type 1 astrocytes able to induce a dopaminergic phenotype in such cells, said contact occurring in the presence of one or more test substances; and

(iii) analysing the proportion of stem or progenitor cells which adopt a dopaminergic fate;

(iv) comparing the proportion of stem or progenitor cells which adopt a dopaminergic fate with the number of stem or progenitor cells which adopt a dopaminergic fate in comparable reaction medium and conditions in the absence of the test substance(s).

51. A method according to claim 50 wherein a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules of such astrocytes, to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr*1 above basal levels, is provided in isolated and/or purified form.

52. A method according to claim 50 or claim 51 wherein a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon, or a molecule or molecules thereof, to induce a dopaminergic fate in neural stem or progenitor cells expressing *Nurr*1 above basal levels, is formulated into a composition comprising one or more additional components.

53. A method according to claim 52 wherein the composition comprises a pharmaceutically acceptable excipient.

54. A method according to claim 53 further comprising administering the composition to an individual.

55. A method according to claim 54 wherein the composition is implanted into the brain of the individual.

56. A method according to claim 55 wherein the